showed five motile larvae per gram of tissue. The two rats fed with the muscle of this patient had motile larvae of *T. spiralis* in their diaphragmatic muscles at the time of autopsy. The two patients treated with thiabendazole had a larval count of 35 and 15 per gram of tissue, respectively. The four rats fed the muscles of these two patients showed no larvae of *T. spiralis* in their muscles at the time of autopsy.

The small number of biopsies prevents us from drawing any conclusions. However, it can be presumed that thiabendazole either had sterilized the larvae in the muscles of the patients or had markedly decreased their virulence. Campbell and Cuckler[5, 6] have already shown this decrease of infectivity in the larvae of *T. spiralis* in swine tested with thiabendazole.

We are grateful to Dr. J. H. Charbonneau, l'Hôpital Pasteur de Montréal, for the charts of the four patients who were admitted to his department. We acknowledge also the assistance of Dr. André Robert, at present bacteriologist at the Maisonneuve Hospital, Montreal, who carried out the larval counts in the biopsy material taken during the convalescent phase and who performed the postmortem examinations of the rats which had ingested muscle specimens from our patients.

RÉSUMÉ

La trichinose humaine

Nous avons observé 11 cas aigus de trichinose humaine: cinq de ces malades ont été traités au thiabendazole. Nous avons passé en revue les données fournies par le laboratoire et décrit l'évolution de la pathologie. Notre étude a permis de montrer que le thiabendazole n'a pas eu d'effet précis sur l'évolution de la trichinose humaine, du moins aux doses employées. Il est cependant possible que le médicament ait pu diminuer l'infectivité des larves qui étaient présentes dans les muscles de nos malades.

Mitral Regurgitation Occurring During Methysergide (Sansert) Therapy

SUMMARY.—The case history of a young woman who developed severe mitral regurgitation after four years of methysergide therapy is reported. Replacement of the mitral valve was required. A brief review of the toxic effects of methysergide is given and special reference is made to lesions of the heart valves that have occurred during methysergide therapy.

Mitral insufficiency in the great majority of cases is due to rheumatic fever with or without superimposed bacterial endocarditis. It may, of course, follow surgical procedures on the valve. In recent years less common etiological factors have become more prominent. These include rupture of a chorda tendinea, infarction with papillary muscle dysfunction, left atrial myxoma, Marfan's syndrome and congenital malformations of the valve leaflets and chordae.

We recently have had under our care a young woman who had severe mitral insufficiency after prolonged use of methysergide for the prevention of migraine. It is our opinion that this drug was the likely etiological agent.

Mrs. C.B.S., aged 40, was first seen by us in November 1966, having been referred for consideration of an open-heart operation on the mitral valve. The patient had been well until the fairly sudden onset of her present symptoms in May 1966. At that time she awakened frequently at night with shortness of breath and had to sit up to obtain relief. When she was examined, a heart murmur was found. Because of increasing dyspnea on effort she was admitted to the Royal Jubilee Hospital in Victoria for investigation by Dr. George Woodwark for mitral insufficiency. From catheter studies it was found that the right ventricular pressure was 62/36 mm. Hg and the left atrial mean pressure was 10 mm. Hg, with a V wave of 28 mm. Hg. Following injection of 75% sodium diatrizoate (Hypaque) into the left ventricle, immediate and gross mitral incompetence was demonstrated. The dye regurgitated into the pulmonary veins as well as into the left atrium. A very small diastolic pressure gradient across the mitral valve was recorded. After this investigation, digoxin was prescribed, with considerable improvement.

Initial Investigation

When seen by us the patient complained of dyspnea on walking around the house and at times when she was lying flat. At other times she would become quite short of breath even while sitting. She had never had hemoptysis or peripheral edema. In addition, she gave an obvious history of hyperventilation with sighing respirations, paresthesias and occasional laryngeal spasm.

Functional enquiry revealed that the patient had suffered from two types of headache. The first was entirely typical of migraine; it occurred as often as weekly and was

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Presented at the Annual Meeting of the Canadian Cardiovascular Society, Vancouver, B.C., November 1968.
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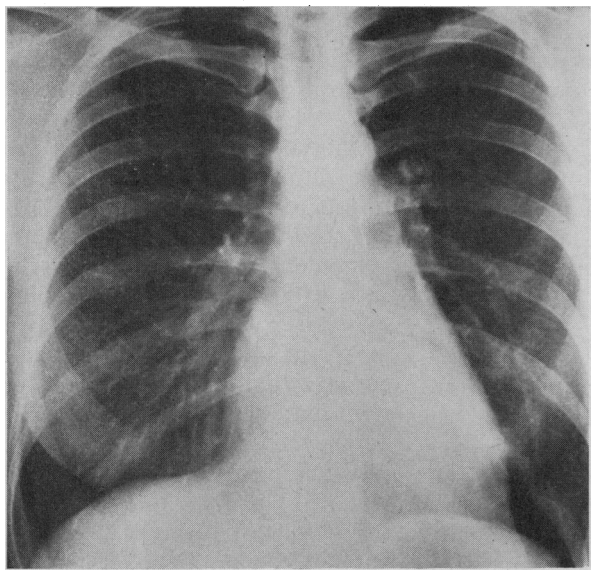

FIG. 1.—Radiograph of heart and lungs immediately before operation.

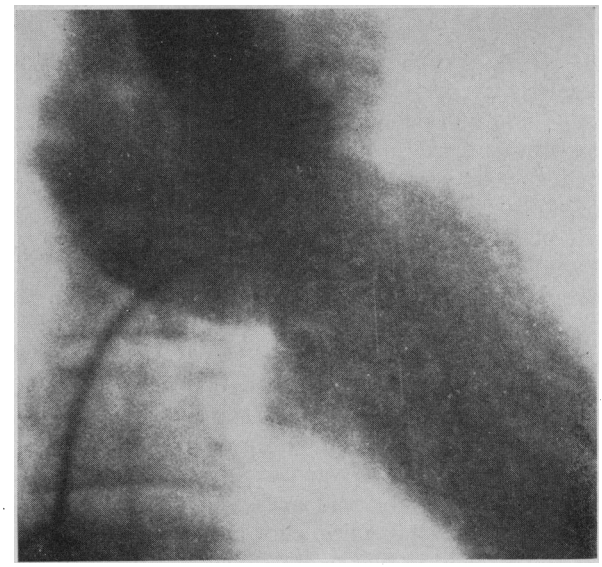

FIG. 2.—Left ventricular angiogram demonstrating marked opacification of the left atrium.

quite severe. The patient stated that for these attacks of migraine she had been taking methysergide (Sansert), 1 mg. three times a day for four years, with great benefit. In addition to migraine, she had had "tension headaches" for many years. Her history included an appendectomy 13 years previously and short episode of pleurisy two years previously. There was no history of rheumatic fever or chorea.

This patient had been examined repeatedly by many physicians over several years. None had found any objective abnormality and, in particular, no heart murmur had been noted until May 1966.

Complete examination was normal in all respects except for the heart. There was no cardiac enlargement, and no thrill or thrust was palpable. There was a grade 3/6 systolic murmur over the precordium, maximal at the apex. It was not pansystolic in duration. There was no diastolic murmur or opening snap. The heart sounds were normal. Radiographs confirmed that the heart was of normal size. No selective chamber enlargement could be recognized but there was some straightening of the left cardiac border. The lung fields were clear. The ECG was normal. Right heart catheterization was repeated in December 1966. The pressure in the right ventricle was 25-27/2-5 mm. Hg and in the pulmonary artery 25/7 mm. Hg. The wedge pulmonary capillary pressure at rest was 10-11 mm. Hg and after three minutes of leg exercise was 19 mm. Hg. Active rheumatic carditis was excluded as far as possible by the absence of anemia and by the presence of a normal sedimentation rate and normal antistreptolysin titre. At this time (December 1966) the conclusion was that the patient had some degree of mitral regurgitation, that she had the hyperventilation syndrome and that she should be kept under observation for a possible cardiac operation. It was strongly recommended that she should stop taking methysergide. Digoxin was continued.

About one month after her discharge from the Vancouver General Hospital, her physician reported that ergotamine tartrate had not successfully controlled her migraine, and that she insisted on resuming methysergide therapy in spite of the risk which she clearly understood.

Second Hospital Admission

Three months later the patient was seen again when her complaints were fatigue and cough at night. She stated that she could walk slowly on the level but had to prop herself up in bed to sleep, because of cough. She also complained of intermittent swelling of the feet and legs which was relieved by chlorothiazide, 500 mg., taken periodically.

The outstanding change on examination was that the apical murmur was now loud and pansystolic in duration. The pulmonic component of the second sound was accentuated. The sedimentation rate and the antistreptolysin titre were again normal. The ECG was normal and the radiograph still did not show any overall cardiac enlargement, but slight left atrial enlargement could be recognized (Fig. 1). Transseptal cardiac catheterization showed normal pressure in the right atrium and right ventricle. The left atrial mean pressure was 11 mm. Hg. The "V" waves were prominent, ranging between 27 and 40 mm. Hg. Left ventricular pressure was 90/5-10 mm. Hg. A left ventricular angiogram demonstrated significant opacification of the left atrium occurring wth the first ventricular systole (Fig. 2), which nearly cleared with atrial contraction. After the angiography, there was a significant increase in the left ventricular end diastolic pressure to 15 mm. Hg and a marked increase in the left atrial "V" waves to 50-60 mm. Hg. Isoproterenol infusion resulted in reduction of the left atrial mean pressure from 25 mm. Hg immediately after angiography to 9 mm. Hg. No other abnormality was found.

The conclusion was that the patient had moderately severe mitral regurgitation due to a ruptured chorda tendinea or to fibrosis from methysergide therapy.

Surgical Management

An open-heart operation was performed on April 27, 1967. Marked mitral regurgitation was found. The chordae tendineae were fused into three large masses on each leaflet. The valve leaflets were very thickened and shiny. The

mural leaflet was adherent to the wall of the ventricle. The septal leaflet was excised. The mural leaflet was left untouched and a Starr valve was sutured in position. The patient's postoperative course was unremarkable. A soft systolic murmur could still be heard at the apex.

Pathological examination showed thickening of the cusps of the valve and shortening and fusion of the chordae tendineae (Fig. 3). No plaques or vegetations were present. Microscopically, marked fibroblastic thickening was noted (Fig. 4). Only minimal vascularization was present and there was no fibrinoid necrosis or fibrin deposit. The chordae showed a tendon-like core surrounded by a good deal of collagen, confirmed by Masson's stain. No central necrosis was seen in the papillary muscle. No rheumatic granulomas were identified.

At the time of discharge the patient agreed not to take any more methysergide.

Subsequent Progress

Six weeks after the operation, readmission to hospital was necessary because of the postcardiotomy syndrome. The patient's immediate response to treatment for this was satisfactory, but she developed increasing heart failure. The clinical suspicion of mitral regurgitation because of a leak in relation to the prosthesis was confirmed by hemodynamic studies and by left ventricular angiograms. A second operation was performed on July 20, 1967, and the regurgitant leak was repaired.

The patient's postoperative course was uncomplicated, but her recovery was slow. When last seen in April 1968 she had numerous symptoms, but it was our opinion that these were not due to her heart. There was no clinical evidence of mitral regurgitation, the ECG showed slight digitalis effect only and the radiograph showed the heart to be at the upper limit of normal in size.

DISCUSSION

In 1956 it was shown by Rowley and Benditt[1] that local injection of 5-hydroxytryptamine (serotonin) into the rat's paw produced edema similar to that produced by the injection of histamine. West[2] found 2-brom-lysergic acid diethylamide to be a specific serotonin antagonist. In 1958 Doepfner and Cerletti[3] reported that "this serotonin edema can be easily blocked by various amide derivatives of lysergic acid". Methyl-derivatives of ergonovine and of methylergonovine proved to have a stronger anti-serotonin effect than the well-known hallucinogenic compound LSD. Sicuteri[4] in 1959 suggested that serotonin and histamine were liberated during an attack of migraine, and he introduced 1-methyl-D-lysergic butanolamide (methysergide) into the therapy of migraine. The drug also has been shown to have a vasoconstricting effect on large arteries and an anti-inflammatory effect. Whatever its precise action is in relation to migraine, it has proved to be the best prophylactic yet discovered.

Side effects

Numerous side effects (Table I) have been reported from the use of the drug.[5-14] Nausea and vomiting are the most common of these, and epigastric pain occasionally occurs. Central nervous system symptoms such as vertigo, depression, euphoria, insomnia and hallucinations have been reported.[10, 11] More serious complications from the use of methysergide include the development of retroperitoneal fibrosis, with or without abdominal masses.[5, 6, 10-13] Spasm or narrowing of major arteries, including the coronary and renal vessels, has been reported.[11] Involvement of the superior mesenteric arteries has been associated with abdominal angina.[8, 9] The Leriche syndrome has been reported.[7] Weight gain, with or without edema of the legs, may occur. Pleuropulmonary fibrosis[14] of considerable degree may develop and may be accompanied by chest pain, fever and by a pleural friction rub. Hypertension may be made worse by methysergide therapy.[10] All of these complications seem to be much less pronounced if the dose is limited to 3 mg. per day.[10] In most cases the complications, no matter how severe, are reversible totally or in part by withdrawal of the drug.

Cardiac lesions

Cardiac lesions related to methysergide therapy include valvular lesions[12, 14] and narrowing of the coronary ostia.[11, 14] Graham[14] has reviewed these cases and his report includes the observations of Dr. Perry MacNeal of Philadelphia. To October 1966 Dr. MacNeal had seen 13 patients who developed cardiac murmurs during methysergide therapy. "Nine of these seem

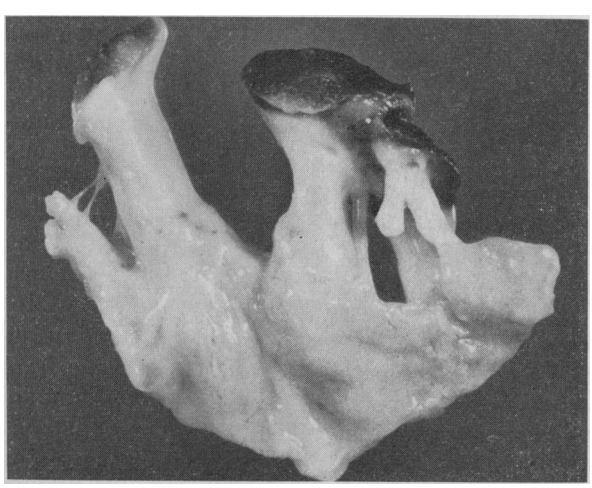

FIG. 3.—Photograph of the anterior leaflet of the excised mitral valve with the thickened, fused chordae tendineae and bits of papillary muscle.

FIG. 4.—Proliferating fibroblasts in subendocardial tissue in the mitral valve.

to have developed mitral insufficiency and four aortic insufficiency. All four of those patients with aortic insufficiency have shown a complete disappearance of their murmurs since discontinuing the use of the drug approximately one year ago. The mitral murmurs, however, seem to remain unchanged."[14]

Graham noted the development of significant heart murmurs in patients on methysergide therapy. Twelve of his reported cases developed aortic insufficiency—in five the murmurs had cleared several months after methysergide was withdrawn. He has collected information on a total of 36 patients (including his own cases and those of MacNeal) who developed cardiac murmurs during methysergide therapy. Some of these had retroperitoneal fibrosis and one had extensive associated bilateral pleuropulmonary fibrosis. These cardiac murmurs were systolic or diastolic and originated at both the mitral and aortic valves. Two of these cases have had open-heart surgery —one had aortic insufficiency and at operation there was a dense fibrous band around the root of the aorta and involving the orifice of the left coronary atery; the aortic valve was replaced by a prosthetic valve. The second case had marked aortic stenosis and regurgitation and mitral stenosis; both valves were replaced, but the patient died the next day.

Present case

It is our belief that in the case we report the lesion of the mitral valve was due to methysergide which the patient had been taking over three years before the onset of cardiac symptoms. She had been examined by many physicians over the years, and no murmur was noted until she rather abruptly developed dyspnea on effort and nocturnal dyspnea. There was no history of rheumatic fever or of allied streptococcal infections and there was no clinical evidence of rheumatic activity subsequent to the onset of her symptoms. None of the specific lesions of acute or chronic rheumatic carditis were seen in the excised valve by the pathologist. This patient would seem to be the third reported case for whom open-heart surgery was required following methysergide therapy.

A further striking feature was the repeated roentgenographic observation of normal heart size and not more than slight left atrial enlargement. The ECG was consistently normal. In spite of the absence of evidence of left ventricular enlargement, this patient had severe angiographically confirmed mitral regurgitation and displayed prominent peaked "V" waves on the direct left atrial pressure recording. Auger and Wigle[15] have described a similar and characteristic clinical and hemodynamic syndrome in patients with previously normal mitral valves who developed abrupt and severe mitral regurgitation due to ruptured chordae tendineae or partial rupture of a papillary muscle.

Precautions in use of methysergide

Methysergide is said to have been used by over one-half million people in the last six years.[14] Its use should be restricted to those in whom migraine is unrelieved by a regimen that includes safer drugs (prophylactic and therapeutic), and in whom the attacks are of such frequency or duration as seriously to upset the individual's life. It has been recommended that the lowest dose compatible with reasonable relief be used and that the therapy should be stopped for one month in each six.[10] Patients who are on methysergide therapy should be under their doctor's close surveillance with particular reference to the development of angina, claudication, a heart murmur, hypertension, loss of peripheral pulses and abdominal pain or masses; the urinary findings should be noted and periodic chest radiographs should be taken. Ergotamine tartrate may still be used for the attack of migraine, and smaller doses are evidently often successful when the patient is on prophylactic methysergide therapy.[10]

Methysergide is contraindicated where there is any definite evidence of atherosclerosis, venous disease, hypertension or peptic ulcer and in pregnancy (Table II).[10] It is also contraindicated in patients with renal or hepatic disease, chronic pulmonary or valvular heart disease and the collagen diseases.[11]

TABLE I.—Methysergide therapy: complications

1.	Weight gain—with or without edema
2.	Gastrointestinal symptoms
3.	Central nervous system symptoms
4.	Retroperitoneal fibrosis
5.	Arterial complications—peripheral
	aortic
	coronary
	renal
6.	Pleuropulmonary fibrosis
7.	Aggravation of hypertension
8.	Cardiac lesions—valvular
	coronary ostial stenosis

TABLE II.—Methysergide therapy: contraindications

1.	Arteriosclerosis—any obvious manifestation
2.	Venous disease
3.	Hypertension
4.	Peptic ulcer
5.	Pregnancy
6.	Renal disease
7.	Hepatic disease
8.	Chronic pulmonary disease
9.	Valvular heart disease
10.	Collagen disease
11.	Other fibrotic disease—Dupuytren's
12.	Septic and cachectic states

RÉSUMÉ

Régurgitation mitrale survenue pendant une cure au méthysergide (Sansert)

Les auteurs relatent l'histoire clinique d'une jeune femme qui a présenté une régurgitation mitrale sévère après un traitement de quatre années au méthysergide. Il a fallu remplacer la valvule mitrale. Ils passent brièvement en revue les effets toxiques du méthysergide et attirent particulièrement l'attention sur les lésions des valvules cardiaques qui sont survenues pendant des cures avec ce médicament.

We are grateful to Dr. John Fairley of Comox, B.C., who was the primary physician in this case. We also acknowledge the contribution of Dr. George Woodwark of Victoria, B.C., who carried out the original hemodynamic studies on our patient. Dr. John R. Graham of Boston has been most helpful in supplying information based on his extensive experience with methysergide and its complications.

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